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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/091,258	03/05/2002	David R. Hathaway	P03660US7	8234

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EXAMINER	
LIU, SAMUEL W	
ART UNIT	**PAPER NUMBER**
1653	

DATE MAILED: 08/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/091,258	HATHAWAY ET AL.	
	Examiner	Art Unit	
	Samuel W Liu	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *28 June 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) *none* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the claims

Claims 1-11 are pending.

Applicants' amendment filed 28 June 2004, which cancels claims 1-4, 9 and 11 has been entered. Also, applicants' request (filed July 2, 2004) for extension of time of one month has been entered.

The following Office Action is applicable to the pending claims1-11. Please note that grounds of objection and/or rejection not explicitly restated and/or set forth below are withdrawn.

Claim Rejections - 35 USC § 112, the first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-11 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The specification as originally filed does not provide support for the invention as now claimed.

The specification fails to provide sufficient description as to use of variants, fragment, analog, mimetics or/and derivative of GLP-1 or analog thereof, or, exendin-4, for treatment or prevention of intermittent claudication (IC) that is caused by or associated with atherosclerosis-

related peripheral vascular disease (PVD). Nowhere in the specification has reasonably provided a written description of how to prevent an intermittent claudication (IC).

Application has disclosed only the method of GLP-1 treatment *cardiac* muscle ischemia disorder state, but not method of GLP-1 treatment or prophylaxis of IC condition that is caused by or associated with peripheral vascular disease (PVD). The skilled artisan, thus, cannot envision contemplated treatment or prophylaxis of the IC condition with *a molecule*, e.g., variants, fragment, analog, mimetics or/and derivative of GLP-1, and would not have known how to extend the result from the treatment of *cardiac* muscle ischemia to treatment or prophylaxis of IC condition associated with skeletal muscle injury. Consequently, conception cannot be achieved until a representative description of such the treatment or prophylaxis stated above, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993).

One of skill in the art would reasonably conclude that the instant disclosure fails to provide written description regarding therapeutic use of a molecule, e.g., GLP-1 variants, fragment, analog, mimetics or derivative. Thus, Applicant was not in a possession of the claimed method.

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

The applicants' response to the rejection under 35 USC 112, the 1st paragraph

The response filed June 28 2004 argues that applicants has possession of the claimed invention as the application has provided (i) a description, in page 3, line 6 to page 6, line 9, of the problem related to said IC condition; (ii) a description, in page 9, line 16 to page 10, line 19 and page 20, lines 1-29, of a solution and reasoning behind the invention (see page 12 the 3rd paragraph of the response).

The applicants' argument has been fully considered but found to be unpersuasive because of the following reasons. (1) Nowhere does in page 3, line 6 to page 6, line 9 of the specification teach use of GLP-1, or variant, fragment, analog, mimetics or derivative thereof to resolve problem of the IC condition. (2) The specification at page 9, line 16 to page 10, line 19 describes a role of GLP-1 in regulation of plasma homeostasis but is not directed to the claimed treatment or prevention of said IC condition. (3) At page 20, lines 1-29, the specification teaches peptide synthesis and purification of GLP-1 molecule but not treatment or prevention of said IC condition as claimed in the instant application. Thus, the specification does not provide any evidence or reasoning behind the invention which allows the skilled artisan to practice the claimed method.

The response also argues that applicants are in possession of *preventing* the IC condition that is caused by PVD state as the instant application is directed to preventing the injury to skeletal tissue caused by ischemia-reperfusion; and thus, by ameliorating or preventing the ischemic-reperfusion injury to skeletal tissue, IC itself may be prevented (see page 13, the 2nd paragraph of the response). Further, the response argues that the examples using *cardiac* muscle exemplify the *broader* teachings relating to ischemia-reperfusion injury to tissues which can be prevented by GLP-1, a fragment, variant, analog, mimetics or derivative thereof, and thus infers

that applicants have provided sufficient information for the skilled artisan to understand the amelioration or preventing the ischemia-reperfusion induced skeletal muscle injury; thereby, the IC condition can be ameliorated or prevented (see page 13, the last paragraph of the response). The applicants' arguments are found to be not persuasive because (i) as stated *supra*, the specification does not teach preventing ischemic disorder of skeletal muscle to which the IC condition may be related; (ii) pathological mechanism of ischemia-reperfusion that causes *skeletal* muscle injury differs from that of *cardiac* muscle ischemia (i.e., myocardial ischemia); and thus, result of *treating myocardial* ischemia cannot be extended to that of *preventing* ischemia-reperfusion caused *skeletal* muscle injury to which development of the IC condition may be related. Thus, it is concluded that the current disclosure does not provide sufficient description of treating or preventing the IC condition which is peripheral vascular disease (PVD).

Claims 1-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating myocardial (i.e., cardiac muscle) ischemia with GLP-1 peptide does not reasonably provide enablement for a method of treatment or prophylaxis of intermittent claudication (IC) condition which is associated with atherosclerosis-related *peripheral* vascular disease (PVD) comprising administering to a subject *a molecule*, i.e., variants, fragment, analog, mimetics or/and derivative of GLP-1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400,

1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

The current application does not provide factual indicia including clinical evidence, guidance as to treating or preventing the IC condition comprising administering to a subject the claimed composition, a molecule, e.g., *variants, agonist, fragment, analog, mimetics or/and derivative of GLP-1*. The specification provides no working example or/and guidance of treating the IC condition using said molecule which broadly any possibilities of structural alterations of GLP-1 peptide. It is noticeable that not all variants or mimetic or analog of GLP-1 can function same as full-length GLP-1 peptide. For instance, it has been shown that a variant GLP-1 (9-39) (an inverse agonist) has adverse biological/pharmacological effect on GLP-1 action (see Serre, V. et al. (1998) *Endocrinol.* 139, 4448-4454). Thus, ability of the GLP-1 *variants, agonist, fragment, analog, mimetics or/and derivative* for treating or preventing the IC condition is unpredictable. Undue experimentation is, therefore, required for sorting out suitable molecule for the treatment or prevention. Therefore, the claim language "fragment, variants, analog, mimetic, agonist, or derivative thereof" would render the claims so broad that the scope of claims is outside the bounds of the enablement and would have resulted in the necessity of undue experimentation.

Because the disclosure does not enable the claimed method of *treating* the IC condition comprising administering to a subject said molecule, the specification is not enabling for *preventing* the same.

The general knowledge and level of skilled in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe how the claimed molecule, i.e., a fragment, variants, analog, mimetic, agonist, or derivative derived from full-length GLP-1 peptide has same or similar pharmaceutical efficacy in both treatment and prophylaxis. Thus, one of skill in the art is required to perform undue experimentation to conduct pharmacological study and prevention trail for the IC condition using the claimed molecule.

In addition, in the absence of experimental data for IC prevention and treatment use of a molecule (a fragment, variants, analog, mimetic, agonist, or derivative derived from GLP-1), the results of clinical investigation with respect to cytotoxicity of the molecule to the subject, it would take undue trials and errors to practice the claimed invention. Moreover, it is of note that dosage for prophylaxis may quite differ from that for treatment. Thus, the quantity of experimentation thus would be large and unpredictable.

In re Fisher, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. The specification does not adequately teach how to effectively prophylaxis/treatment of the IC condition or reach any therapeutic endpoint in humans by administering said molecule. The specification does not teach how to extrapolate data obtained from "effect of GLP-1 on cardiac muscle ischemia in dog to human. Note that the current application claims that said subject is human (see claim 10). Therefore, it is not clear that the skilled artisan could predict the efficacy of the administered molecule set forth in the specification.

In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view of the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Wei Liu whose telephone number is 571-272-0949.

The examiner can normally be reached from 9:00 a.m. to 5:00 p.m. on weekdays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber, can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 703 308-4242 or 703 872-9306 (official) or 703 872-9307 (after final). Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 305-4700.

Samuel Wei Liu, Ph.D.

August 10, 2004

KAREN COCHRANE CARLSON, PH.D
PRIMARY EXAMINER